Original Research

Devil's Claw (*Harpagophytum procumbens*): no evidence for anti-inflammatory activity in the treatment of arthritic disease

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Devil's Claw (*Harpagophytum procumbens*), an herbal product being marketed in Canada as a home remedy for the relief of arthritic disease, was screened for efficacy with standard preclinical screening methods. At doses 100 times or greater than the recommended daily dose for humans, Devil's Claw was completely ineffective in reducing edema of the rat hind foot induced by either λ-carrageenan or *Mycobacterium butyricum*. At concentrations of up to 1×10^5 μg/ml, Devil's Claw was also ineffective as an in-vitro inhibitor of prostaglandin synthetase. These results indicate that Devil's Claw lacks the anti-inflammatory properties possessed by all antiarthritic drugs of the nonsteroidal, anti-inflammatory analgesic type.

La Griffe du Diable (*Harpagophytum procumbens*), un produit d'herboristerie vendu au Canada comme un remède maison pour le soulagement des maladies arthritiques, a été soumise à des épreuves d'activité par les méthodes standards de prospection systématique utilisées au stade pré-clinique. A des doses 100 fois supérieures, ou plus, à celles qui sont recommandées chez l'humain, la Griffe du Diable était totalement inactive dans le test de l'oedème de la patte postérieure provoqué par la λ-carragénine ou le *Mycobacterium butyricum*. A des concentrations allant jusqu'à 1×10^5 μg/ml la Griffe du Diable était également inefficace comme inhibiteur in vitro de la prostaglandine synthétase. Ces résultats indiquent que la Griffe du Diable est dépourve des propriétés anti-inflammatoires que possèdent tous les anti-arthritiques de type anti-inflammatoire analgésique non-stéroïdien.

Devil's Claw, an herbal product prepared from the secondary lateral roots of *Harpagophytum procumbens*, is being marketed in Canada principally in health food stores as a home remedy for the treatment of arthritic symptoms. The major active component of Devil's Claw is thought to be harpagoside, a monoterpenic glucoside belonging to the iridoid class of compounds.[1] Views concerning the safety and efficacy of Devil's Claw have generally been based upon folklore and testimonials.

Studies in our laboratory indicated that various commercial sources of Devil's Claw extract contained 1.4% to 2.0% harpagoside, confirming figures previously reported (1.5% to 1.7%).[2] Caprasse[2] indicated that Albus had found the average oral lethal dose (LD) in mice to be 220 ml/kg of what was presumably a 10% aqueous solution of Devil's Claw extract. Preliminary studies in our laboratory indicated that in male and female Swiss Webster mice the acute LD_0 and LD_{50} of Devil's Claw were greater than 13.5 g/kg.

In male Wistar rats the clinical, hematologic and gross pathological findings were unremarkable following 21 days of treatment with 7.5 g/kg of Devil's Claw, given orally, and subtle hepatic effects could not be demonstrated by changes in liver weight or levels of microsomal protein, cytochrome P_{450}, cytochrome b_5, reduced nicotinamide adenine dinucleotide phosphate-cytochrome *c* reductase, ethylmorphine-*N*-demethylase, nitroreductase or azoreductase after 7 days of treatment with 2.0 g/kg given orally. No chronic toxicity studies have been done, and the acute and subacute studies are by no means exhaustive, but the data available from animals do suggest that Devil's Claw extract is of low toxicity in the short term.

In recent years Devil's Claw has received wide acceptance in both Canada and Europe as a treatment for arthritic disease. In 1976, 30 000 arthritic patients were using Devil's Claw in Great Britain alone.[3] Since the efficacy and widespread use of Devil's Claw is predicated, at best, on very limited scientific information, our aim was to examine the efficacy of Devil's Claw as an antiarthritic agent using three standard preclinical methods of screening anti-inflammatory agents.

Materials and methods

Male Sprague–Dawley rats (Canadian Breeding Farms Ltd., St. Constant, PQ), weighing 160 ± 20 g,

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were acclimatized to the laboratory for 1 week and then assigned to treatment groups within two of the three parts of the study (Tables I and II). We adhered to the guidelines of the Canadian Council on Animal Care. The third part of the study was solely a biochemical assay.

Carrageenan-induced edema

We pretreated the animals with one or the other of two anti-inflammatory agents (Devil's Claw, 20 to 6000 mg/kg, and acetylsalicylic acid [ASA], 200 mg/kg) administered by gastric gavage at a rate of 20 ml/kg. One hour later we injected 0.05 ml of a 1% (weight/volume) aqueous solution of λ-carrageenan (Sigma Chemical Co., St. Louis, Missouri) into the plantar tissue of each animal's right hind foot. The volumes of the right and left hind feet were measured by mercury displacement before and 3 hours after carrageenan treatment, as previously described.[4]

Adjuvant-induced arthritis

On day 0 we injected 0.05 ml of *Mycobacterium butyricum* (15 mg of killed bacteria per millilitre of mineral oil) into the right hind paw of all rats except the controls. Edema in the contralateral foot was monitored in each animal, and on day 11 all adjuvant-pretreated animals exhibiting a foot volume of 2.00 ml or more were randomly divided into three treatment groups. The rats accordingly received water, 2 ml/kg, Devil's Claw, 2 g/kg, or indomethacin, 3 mg/kg, daily. We monitored the volumes of the feet on days 11, 15 and 17 (days 0, 4 and 6 of treatment with the anti-inflammatory agents) and calculated the mean foot volumes for each treatment and day.

Prostaglandin synthetase inhibition

The assay of prostaglandin synthetase was based upon that of Yoshimoto and colleagues[5] using radiolabelled arachidonic acid as a substrate. Excess arachidonic acid was extracted from the incubation mixture, as previously reported.[6] Prostaglandin synthetase (Miles Laboratories Inc., Elkhart, Indiana; 1.3 U/g) was incubated with radiolabelled arachidonic acid (New England Nuclear, Boston; 1-^{14}C; 0.01 μCi) at 37°C for 4 minutes with and without various concentrations of the potential prostaglandin synthetase inhibitors. The inhibitors we examined were indomethacin, ASA and Devil's Claw. The reaction mixture had a final volume of 2.0 ml and contained TRIS (tromethamine) hydrochloride buffer (0.2 M, pH 8.0), glutathione (1.25 mM), hydroquinone (0.33 mM), hemoglobin (0.5 μM), ^{14}C-arachidonic acid (0.5 mM), the enzyme (0.013 U) and one of the three prostaglandin synthetase inhibitors. At the end of the 4-minute incubation period the reaction was stopped by the addition of 5 ml of hexane-ethyl acetate (2:1). The incubation vials were shaken, centrifuged (at a rate of 625 × *g* for 5 minutes) and then placed in a freezer. The solvent layer was then decanted from the frozen incubation mixture, more solvent was added and the procedure was repeated. One millilitre of the aqueous incubation medium was then transferred to a scintillation vial containing Atomlight (New England Nuclear, Boston; 10 ml) for liquid scintillation counting. The percentage inhibition was calculated as follows:

$$100 - \frac{\text{cpm with inhibitor} - \text{cpm enzyme blank}}{\text{cpm without inhibitor} - \text{cpm enzyme blank}} \times 100$$

where cpm = counts per minute. The incubations were repeated three times for each inhibitor concentration.

Table I—Effect of Devil's Claw and acetylsalicylic acid (ASA) on carrageenan-induced edema in the hind foot of the rat

Anti-inflammatory agent (mg/kg)	n	Volume of foot (ml); mean ± standard error (SE)	% inhibition*
Devil's Claw			
0	6	0.655 ± 0.070	–
20	6	0.625 ± 0.036	4.6
200	6	0.617 ± 0.064	5.8
2000	6	0.522 ± 0.063	20.3
6000	6	0.675 ± 0.054	−3.1
ASA			
0	3	0.630 ± 0.075	–
200	4	0.303 ± 0.011†	51.9

*100 $(1 - V_T/V_C)$ where V_T represents the foot volume 3 hours after the injection of carrageenan in animals treated with an anti-inflammatory agent; V_C represents the volume in the vehicle-treated controls.
†$P < 0.01$ when compared with value for controls.

Table II—Effect of daily oral treatment with water, Devil's Claw or indomethacin on adjuvant-induced edema in the contralateral hind foot of the rat

		Foot volume (ml); mean ± SE			
		Treatment day*			
Treatment	n	0	11	15	17
None†	6	1.66 ± 0.01	1.74 ± 0.02	1.82 ± 0.04	1.82 ± 0.03
Water (2 ml/kg)	6	–	2.32 ± 0.19	2.62 ± 0.20	2.91 ± 0.18‡
Devil's Claw (2 g/kg)	6	–	2.30 ± 0.12	2.76 ± 0.28	3.07 ± 0.26‡
Indomethacin (3 mg/kg)	6	–	2.41 ± 0.16	1.68 ± 0.03‡	–

*On day 0 adjuvant (*Mycobacterium butyricum*) was injected into the right hind foot, and on day 11 anti-inflammatory treatment was initiated.
†Controls were not pretreated with adjuvant and did not receive any anti-inflammatory treatment.
‡$P < 0.05$ when compared with value for day 11 (first day of treatment with the same anti-inflammatory agent).

Analysis

The results were presented as means and standard errors, and differences were tested by the unpaired *t*-test. The concentration of inhibitor causing 50% inhibition (I_{50}) of prostaglandin synthetase was estimated by a logit program based on that of Waud,[7] and the 95% confidence limits were calculated using the probit analysis of Finney.[8]

Results

Carrageenan-induced edema in the hind foot of the rat was not significantly inhibited by Devil's Claw at doses up to 6000 mg/kg but was reduced 51.9% by ASA at a dose of 200 mg/kg (Table I).

Adjuvant-induced arthritis was also unresponsive to treatment with Devil's Claw (2 g/kg daily for 7 days) but was completely alleviated by indomethacin given for 4 days (Table II).

The effects of Devil's Claw on prostaglandin synthetase were examined in vitro. At concentrations up to 1×10^5 μg/ml, Devil's Claw did not significantly alter synthetase activity, whereas indomethacin and ASA, both classic anti-inflammatory agents, caused 50% inhibition of the enzyme at concentrations of 0.316 and 437 μg/ml respectively (Table III).

Discussion

The oral administration of Devil's Claw extract did not alter the development of carrageenan-induced edema in the hind foot of the rats we studied (Table I), confirming a previous report,[9] whereas ASA, 200 mg/kg, reduced the edema by 51.9%, a figure comparable to those in other reports of its effectiveness as determined by this screening method.[4,10]

McLeod and associates[9] showed that in rats with adjuvant (*M. tuberculosis*)-induced arthritis, Devil's Claw produced no significant effects on either the primary (on days 0 through 10) or the secondary (on days 11 through 20) inflammatory reaction when administered daily at a dose of 100 mg/kg. We examined the effects of higher daily doses of Devil's Claw (2 g/kg) on the secondary inflammatory reaction in the rat and demonstrated that, even at doses 100 times the recommended daily dose for humans, Devil's Claw possessed no antiarthritic activity (Table II).

Many nonsteroidal anti-inflammatory agents act by inhibiting prostaglandin biosynthesis. We found that the I_{50} of indomethacin was 0.316 μg/ml and that of ASA 437 μg/ml (Table III), figures comparable to previously reported values.[6] Devil's Claw, however, did not alter the in-vitro activity of prostaglandin synthetase, even at concentrations up to 1×10^5 μg/ml, indicating that the purported anti-inflammatory activity of this herbal product is not mediated by the inhibition of prostaglandin biosynthesis.

The lack of pharmacologic activity observed in these studies of efficacy, together with the fact that Grahame and Robinson[3] could not demonstrate any significant change in 12 arthritic patients in a preliminary 6-week clinical trial, raises questions as to the rationale for the use of Devil's Claw in the treatment of arthritic disease.

Table III—Inhibition of prostaglandin synthetase by indomethacin, ASA and Devil's Claw

Inhibitor (μg/ml)	Inhibition (%)*	I_{50}† with 95% confidence limits (μg/ml)
Indomethacin		
0.05	8.2 ± 4.8	
0.10	24.6 ± 1.6	0.316
0.25	46.2 ± 4.0	(0.297 – 0.335)
0.50	61.1 ± 10.4	
0.75	67.5 ± 3.3	
1.00	75.4 ± 2.8	
ASA		
50	1.2 ± 1.4	
100	15.9 ± 2.0	
250	29.1 ± 2.7	437
500	59.0 ± 4.6	(405 – 472)
750	66.4 ± 2.5	
1000	63.3 ± 5.9	
Devil's Claw‡		
1	5.1 ± 2.6 (98.5 ± 7.6)	
10	2.7 ± 2.6 (106.7 ± 9.2)	
100	7.3 ± 4.5 (100.7 ± 14.7)	
1000	5.0 ± 2.7 (96.5 ± 5.1)	> 100 000
10 000	8.9 ± 2.4 (91.1 ± 3.0)	
100 000	4.7 ± 4.7 (97.7 ± 7.2)	

***Means and SEs from three incubations. Data in parentheses represent the enzyme's activity expressed as a percentage of its activity in the absence of Devil's Claw.**
†I_{50} = concentration of inhibitor causing 50% inhibition of prostaglandin synthetase.
‡Percentage inhibition was calculated using a value of 0% inhibition when the activity in the presence of Devil's Claw was greater than the activity in the absence of Devil's Claw.

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